

What is Claimed:

1. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 150 to about 325 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, and includes at least one peptide-bonded polypeptide of about 6 to about 24 residues of the influenza A M2 polypeptide of SEQ ID NO:9 wherein

(a) Domain I comprises (i) about 75 to about 110 amino acid residues whose sequence includes at least the sequence of the residues of position 4 through position 75 of HBc, (ii) one to three cysteine residues present at a position in the chimer molecule of about one to about -20 relative to the N-terminus of HBc of SEQ ID NO:1 [N-terminal cysteine residue(s)], said one or more N-terminal cysteine residues being present within a sequence other than that of the pre-core sequence of HBc, and optionally includes said sequence of about 6 to about 24 residues of the influenza A M2 polypeptide of SEQ ID NO:9 that, when present, is peptide-bonded to or within about 15 residues of the N-terminus of the HBc sequence,

(b) Domain II comprises about 10 to about 60 amino acid residues peptide-bonded to residue 75 of which (i) zero to all of the sequence of HBc is present from position 76 through 85 and (ii) an optional sequence of 6 to about 48 residues that constitute one or more repeats of the influenza A M2 polypeptide of SEQ ID NO: 9;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

d) Domain IV comprises (i) the residues of positions 136-140 plus up to nine residues of an HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) zero to three cysteine residues, and (iii) up to about 100 amino acid residues in a sequence heterologous to HBc from position 164 to the HBc C-terminus;

said chimer molecule (i) containing no more than 10 percent conservatively substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles being more stable on formation than are particles formed from an otherwise identical HBc chimer that lacks said N-terminal cysteine residue(s) or in which an N-terminal cysteine residue present in the chimer molecule is replaced by another residue.

2. The recombinant HBc chimer protein molecule according to claim 1 wherein one of said residues X₁₇ and X₁₉ of said M2 polypeptide of SEQ ID NO:9 is cysteine.

3. The recombinant HBc chimer protein molecule according to claim 1 wherein said M2 polypeptide of SEQ ID NO:9 includes residues X₂ through X₂₄.

4. The recombinant HBc chimer protein molecule according to claim 1 wherein M2 polypeptide of SEQ ID NO:9 is present in Domain I.

5. The recombinant HBc chimer protein molecule according to claim 1 wherein M2 polypeptide of SEQ ID NO:9 is present in Domain II.

6. The recombinant HBc chimer protein molecule according to claim 1 wherein Domain I consists essentially of the HBc sequence from position 2 through position 75.

7. The recombinant HBc chimer protein molecule according to claim 1 wherein Domain IV contains zero cysteine residues.

8. The recombinant HBc chimer protein molecule according to claim 1 wherein Domain IV is free of said sequence heterologous to HBc at position 164 to the C-terminus.

9. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a sequence of about 155 to about 225 amino acid residues that contains four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, and includes at least one peptide-bonded polypeptide of about 6 to about 24 residues of the influenza A M2 polypeptide of SEQ ID NO:9 wherein

(a) Domain I comprises (i) about 95 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 4 through position 75 of HBc, (ii) one to three

cysteine residues present at a position in the chimer molecule of about one to about -14 relative to the N-terminus of HBc of SEQ ID NO:1 [N-terminal cysteine residue(s)], said one or more N-terminal cysteine residues being present within a sequence other than that of the pre-core sequence of HBc, and optionally includes said sequence of about 6 to about 24 residues of the influenza A M2 polypeptide of SEQ ID NO:9 that, when present, is peptide-bonded to or within about 15 residues of the N-terminus of the HBc sequence,

(b) Domain II comprises about 10 to about 60 amino acid residues peptide-bonded to residue 75 of which (i) zero to all of the sequence of HBc is present from position 76 through 85 and (ii) an optional sequence of 6 to about 48 residues that constitute one or more repeats of the influenza A M2 polypeptide of SEQ ID NO: 9;

(c) Domain III consists essentially of the HBc sequence from position 86 through position 135; and

d) Domain IV comprises (i) the residues of positions 136-140 plus up to nine residues of an HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) zero or one cysteine residue, and (iii) up to about 50 amino acid residues in a sequence heterologous to HBc from position 164 to the HBc C-terminus;

said chimer molecule (i) containing no more than 5 percent conservatively substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and

said particles being more stable on formation than are particles formed from an otherwise identical HBC chimera that lacks said N-terminal cysteine residue(s) or in which an N-terminal cysteine residue present in the chimera molecule is replaced by another residue.

10. The recombinant HBc chimer protein molecule according to claim 9 wherein Domain IV includes a sequence of about nine amino acid residues of the HBc sequence from residue position 141 through about position 149 peptide-bonded to residue 140.

11. The recombinant HBc chimer protein molecule according to claim 9 wherein Domain I includes one N-terminal cysteine residue.

12. The recombinant HBc chimer protein molecule according to claim 9 wherein Domain IV includes one C-terminal cysteine residue.

13. The recombinant HBc chimer protein molecule according to claim 9 wherein Domain I includes one N-terminal cysteine residue and Domain IV includes one C-terminal cysteine residue.

14. The recombinant HBc chimer protein molecule according to claim 9 wherein one of said residues X₁₇ and X₁₉ of said M2 polypeptide of SEQ ID NO:9 is cysteine.

15. The recombinant HBc chimer protein molecule according to claim 9 wherein said M2 polypeptide of SEQ ID NO:9 includes residues X₂ through X₂₄.

22. Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules according to claim 9.

23. Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules according to claim 22 that include the C-terminal 23 residues of the influenza A M2 polypeptide of SEQ ID NO: 9..

24. A vaccine or inoculum comprising an immunogenic effective amount immunogenic particles according to claim 1 dissolved or dispersed in a pharmaceutically acceptable diluent.

25. A vaccine or inoculum comprising an immunogenic effective amount immunogenic particles according to claim 9 dissolved or dispersed in a pharmaceutically acceptable diluent.

26. A nucleic acid that encodes a recombinant HBc protein molecule according to claim 1, or a variant, analog or complement thereof.

27. A nucleic acid that encodes a recombinant HBc protein molecule according to claim 9, or a variant, analog or complement thereof.

28. A recombinant nucleic acid molecule that comprises a vector operatively linked to a nucleic acid segment defining a gene that encodes a recombinant HBc protein molecule according to claim 1, or a varient, analog or complement thereof, and a

promoter suitable for driving the expression of the gene in a compatible host organism.

29. A recombinant nucleic acid molecule that comprises a vector operatively linked to a nucleic acid segment defining a gene that encodes a recombinant HBc protein molecule according to claim 9, or a variant, analog or complement thereof, and a promoter suitable for driving the expression of the gene in a compatible host organism.

30. A host cell transformed with a recombinant nucleic acid molecule according to claim 28.

31. The transformed host cell according to claim 30 wherein said host cell is selected from the group consisting of *E. coli*, *S. typhi*, *S. typhimurium* and a *S. typhimurium-E. coli* hybrid.

32. A host cell transformed with a recombinant nucleic acid molecule according to claim 29.

33. The transformed host cell according to claim 32 wherein said host cell is selected from the group consisting of *E. coli*, *S. typhi*, *S. typhimurium* and a *S. typhimurium-E. coli* hybrid.